

REMARKS

Claim 18 has been amended. Claims 1-17 and 22-24 were previously canceled. Support for the amendments is found in the existing claims and the specification. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Rejections withdrawn

Applicant gratefully acknowledges withdrawal of the previous rejection under 35 U.S.C. § 103(a).

Rejection under 35 U.S.C. § 103(a)

Claims 18-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Critchley (2002), Buck, et al. (1999), and Mackay, et al. (2002) as evidenced by Froguel, et al. (1993) and Howell, et al. (1999).

Critchley, et al. teach melting curve analysis and teach a sequence of 480 bases that includes SEQ ID NOS: 21 and 22.

Claim 18 has been amended to specify that “the nucleic acid probe ~~has~~ consists of the nucleotide sequence of SEQ ID NO: 21 or 22. SEQ ID NOS: 21 and 22 contain 16 and 18 nucleotides, respectively. The Office Action characterizes Critchley, et al. as “Critchley does not specifically teach sequences consisting of SEQ ID NO: 21 or SEQ ID NO:22 and does not specifically teach a nucleic acid probe having a 3’ terminal cytosine labeled with a fluorophore” (Office Action, page 4, 1st paragraph under sequence comparison). The claims have been amended to the closed language “consisting of” which the Examiner concedes is not taught by Critchley, et al. The claims were also previously limited to “having a 3’ terminal cytosine labeled with a fluorescent dye” which is also not taught by the primary reference.

The Examiner cites upon *In re Deuel* 34 USPQ2d 1210 (Fed Cir 1995) as teaching that “normally a *prima facie* case of obviousness is based upon structural similarity...a prior art compounds may suggest its homologs” (Office Action, page 5).

The Examiner asserts that the claimed probes are structural homologs of the sequences of Critchley, et al. However, the 480 base pair segment referenced by the Examiner (SEQ ID NO: 13) is merely a segment of the human mitochondrion complete genome which includes the A3243G mutation (segment 3001-3480, see page 6, paragraph 5 of Critchley, et al. referring to Figure 6). This 480 base pair segment is not a probe and does not correspond to the probes claimed by Applicants because it is 462-464 base pairs longer than the probes of Applicant's claimed method. Accordingly, Applicant asserts that the present claims are non-obvious in view of Critchley, et al. taken with the secondary and tertiary references which will be discussed below.

However, even if the Examiner's view is accepted, as stated in M.P.E.P. 716.02(a), "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985)". In the present case, "a greater than expected result" has been shown as evidenced by the data in the specification. Among many possible probes for detection of the mitochondrial DNA 3243 mutation, Applicant has discovered that a nucleic acid probe with the 3' end as cytosine corresponding to position 230 as shown in SEQ ID NO: 2, such as SEQ ID NOS: 21 and 22, is important. Specifically, as shown in Figure 5, the probes of the present invention (i.e., SEQ ID NOS: 21 and 22) were able to detect the mitochondrial DNA 3243 mutation, while other probes could not (Figure 4). The specification describes that only when the probes 3T-mt-R2-18, 3T-mt-R2-17, 3FL-mt-R2-18 and 3FL-mt-R2-17 (probes corresponding to SEQ ID NOS: 21 and 22, see Table 9) were used, changes in fluorescence intensity that could be analyzed by Tm analysis were observed (present specification, page 29, lines 2-5, after the flow chart). Accordingly, even if one takes the view that the Office Action presents a *prima facie* case of obviousness, this position is rebutted by greater than expected results for the method when using the probes corresponding to SEQ ID NOS: 21 and 22.

Buck, et al. is cited as evidence of equivalence of primers. However, the data from the specification discussed above directly rebuts the teaching of Buck, et al. SEQ ID NOS: 13, 14, 15, 16, 17, 18, 19, and 20 (Applicant's specification, page 28; Figure 4) were not effective as probes. Therefore, all sequences clearly are not equivalent, at least for the claimed probes SEQ ID NOS 21 and 22 of the claimed method. Furthermore, Buck, et al. are directed to primers, not

probes and to sequencing, not melting curve analysis. The Examiner does not explain why the teaching of Buck, et al. on primers and sequencing can be extrapolated to a different biochemical method.

Critchley, et al. also fail to teach “a nucleic acid probe having a 3’ terminal cytosine labeled with a fluorescent dye” (claim 18). Mackay, et al. is newly cited to supply this teaching. However, Mackay, et al. do not teach the specifically claimed probes. Mackay, et al. do not teach a 3’ terminal cytosine of a probe corresponding to nucleotide number 230 of SEQ ID NO:2¹. As discussed above, probes other than the probes of SEQ ID NOS: 21 and 22, in which the 3’ terminal cytosine of the probes of SEQ ID NOS: 21 and 22 corresponds to nucleotide number 230 of SEQ ID NO: 2, were unable to detect the mitochondrial DNA 3243 mutation. Accordingly, Mackay, et al. do not correct the deficiencies of Critchley, et al. and Buck, et al.

Howell, et al is cited for teaching in more detail the DASH method of Critchley, et al. (page 3 and 4 of Office Action) and Froguel is cited for teaching PCR methods (page 4 of Office Action). The cited references taken as a whole do not teach or suggest the claimed invention which is a method using “a 3’ terminal cytosine labeled with a fluorescent dye and ...detecting the mutation on the basis of the result of the melting curve analysis, wherein ...the nucleic acid probe ~~has-consists of~~ the nucleotide sequence of SEQ ID NO: 21 or 22” (claim 18). None of the cited references teach probes corresponding to SEQ ID NOS: 21 or 22. Accordingly, Applicant asserts that the present claims are non-obvious over the cited references.

However, even if a *prima facie* case of obviousness has been made, the *prima facie* case is rebutted by the evidence from Applicant’s specification discussed above. As discussed above and shown by the data of the specification, from among the probes tested, only probes corresponding to SEQ ID NOS: 21 and 22 provided changes in fluorescence intensity that could be analyzed by Tm analysis (Applicants’ specification, page 29, lines 1-5 after flow chart)

In view of Applicant’s amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

¹ Note that although claim 18 does not specifically recite nucleotide number 230, claim 18 originally referred to claim 16 which included this recitation. In response to the species election of SEQ ID NOS: 20 and 21, claim 18 was amended to recite these sequences which inherently include this feature (see claim objection on page 3 of paper no. 20071017).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Application No.: 10/553,576
Filing Date: October 17, 2005

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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